REMARKS

The Rejections Under 35 U.S.C. 112, First Paragraph-Lack of Enablement

Claims 246-270 have been rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. It is asserted that the scope of the invention has not changed by the addition of new claims such that one of skill in the art would not face the same problems as addressed with prior claims 1-24 and 245. In the Examiner's view, the new claims are broadly drawn to any non-naturally occurring non-native polynucleotide construct having very broad limitations. As such, the Examiner concludes that the breadth of possible constructs is not considered enabled by one skilled in the art at the time the invention was made.

Furthermore, it is asserted that Applicant does not further address the enablement of the claimed constructs applied to whole organisms as broadly claimed. The Office Action dated 2/3/99 states that there is a high levelof unpredictabiiity in the antisense art and analogous gene therapy art for in vivo (whole organism). In the Examiner's view, barriers to successful delivery of antisense to the organism are : (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus (2) withstanding enzymatic degradation and (3) the ability to find and bind the target site and simultaneously avoiding non-specific binding. The Office Action cites passages from Branch and Flanagan as evidence of skepticism of those of skill in the art.

Applicants respectfully traverse the rejection and will address each of the points made. First, in Applicants view, it would not require undue experimentation for the ordinary skilled artisan to practice the invention. A sufficiently detailed description is provided in the specification for obtaining the constructs of the present invention on pages 17-18, 34-47. Working examples are provided in Examples 1-5. Applicants attach hereto a decision tree provided with "Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph-Enablement Chemical/Biotechnical Applications. Two questions are posed in the decision tree. The first is "Does the specification teach how to make and use at least one embodiment encompassed by the claims as a whole without undue experimiantion?" Clearly, the specification has taught one of ordinary skill in the art how to make and use more than one embodiment. The second question is "Are the enabled embodiments representative of the full scope of the claims?" Again the answer is yes. The methods described for obtaining the disclosed constructs could be applied to obtaining any of the constructs encompassed by the pending claims.

Second, Applicants note that the scope of the presently pending claims, 246-270 are directed to constructs, not to a method. Therefore, the issue of whether or not the use of the claimed costructs is enabled only in vitro or in vivo is not determinative under the standard applied pursuant to 35 U.S.C. §§101 or 112, first paragraph given that it is acknowledged in the Office Action that Applicants have provided examples that show antisense inhibition of HIV in infected U937 cell culture using various U1 constructs, expression of A, B an dC antisense by hybridization analysis after expression of the U1 clone, and expression of the

fusion product antisense A upstream of B-gal gene where antisense activity of the A portion cause inhibiton of B-gal activity in lacZ assays (Figure 51).

Third, Applicants note that Branch and Flanagan, which was cited in the Office Action dated 2/8/99 was actually published **after** the priority date of the above-referenced application. The MPEP in Section 2164.05(a) states that "the state of the art existing at the filing date of the application is used to determine whether a particular disclosure is enabling as of the filing date." This section further states "In general, the examiner should not use post-filing date references to demonstrate that the patent is non-enabling." Applicants nevertheless assert that there are a number of publications available as of the priority date of the above-referenced application as well as publications published after the priority date of the above-referenced application which express a more optimistic attitude regarding the suitability of antisense to become useful in therapeutic application. One example of such a publication is Crooke, 1994, Antisense Research and Development 4:145-6, attached hereto as Exhibit 1.

It is also Applicants' position that *in vivo* data is not necessary. As noted in the MPEP Section 2107.03, III, "Office personnel should be careful not to find evidence unpersuasive simply because no animal model for the human disease condition had been established prior to the filing of the application.

In view of the above arguments, Applicants assert that the pending claims do meet the enablement requirements of 35 U.S.C. §112, first paragraph. Therefore, Applicants respectfully request that the rejections be withdrawn.

The Rejections Under 35 U.S.C. 112, First Paragraph-Written Description

Claims 245-262, 267-280 and 285-298 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. It is asserted that the specification as filed teaches only prophetically the majority of the constructs for the breadth claimed, and does not clearly describe to one skilled in the art that the inventor was in possession of the genus of claimed constructs considering the high level of unpredictability in the gene therapy and antisense art, the suggested applications for the prophetic constructs taught for producing a product in a cell, such as antisense.

Applicants respectfully traverse the rejection. The Final Written Description Guidelines state in Paragraph II.A.3.a.

> Possession may be shown in many ways. For example, possession may be shown, inter alia, by describing an actual reduction to practice of the claimed invention. Possession may also be shown by a clear depiction of the invention in detailed drawings or in structural chemical formulas which permit a person skilled in the art to clearly recognize that applicant had possession of the claimed invention. An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention.....
>
> An applicant may show possession of an invention by disclosure of drawings \39\ or structural chemical formulas\40\ that are sufficiently detailed to show that

applicant was in possession of the claimed invention as a whole. The description need only describe in detail that which is new or not conventional.\41\ This is equally true whether the claimed invention is directed to a product or a process.

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics \42\ which provide evidence that applicant was in possession of the claimed invention,\43\ i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.\44\ What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.\45\ If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.\46\

The Written Description Guidelines further state in paragraph II.A.3.a.(2)

(2) For each claim drawn to a genus:

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice ....., reduction to drawings ....., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus (citiation omitted).

> A ``representative number of species'' means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. On the other hand, there may be situations where one species adequately supports a genus (citation omitted). What constitutes a ``representative number'' is an inverse function of the skill and knowledge in the art.
>
> Satisfactory disclosure of a ``representative number'' depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed. For inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus (citation omitted).
>
> Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces (citation omitted). If a representative number of adequately described species are not disclosed for a genus, the claim to that genus must be rejected as lacking adequate written description under 35 U.S.C. 112, para. 1.

Applicants assert that an adequate description has been provided. A detailed description of the constructs of the present invention are provided throughout the specification, particularly on pages 33-47. The terms "primary nucleic acid construct", "production center", "propagation", "production" and "inherent cellular systmes" is provided on page 53. The properties of the constructs of the present invention are provided on page 34, lines 9-16. It is further stated in the sentence bridging page 34 and 35:

> A construct modified by the addition of ligands or chemical modifications could further complex with other moieties, those moieties being natural or unnatural, modified or unmodified oligo- or polypeptides; polycations; natural or unnatural, modified or unmodified oligo- or polysaccharides; multimolecular complexes; inactivated viruses; and any chemical binding, attachment or conjugation capable of complexing with the ligand or chemical moiety.

The only complete paragraph on p. 35 describes how chemical modifications can be localized to regions of the construct. It is noted that the modifications may or may not interfere with biological activity.

The paragraph bridging pages 35 and 36 state that the construct comprises at least one modified nucleotide, a nucleotide analog and a non-nucleic acid entity. A description of each of these components is provided on pages 36-38 (first paragraph). A description of the nucleic acid component of the construct of the present invention are provided on pages 38-39. Means of attaching ligands or chemical modifications is provided on pages 39-41. Examples of cell targeting entities, entities which facilitate cellular uptake, entities specifying intracellular localization, entities which facilitate incorporation into cellular nucleic acid and entities which impart nuclease resistance are provided on pages 42-44. Methods for introducing ligands or chemical modifications in the constructs of the present invention are disclosed in the paragraph bridging pages 44 and 45.

The disclosures in the specification clearly conform to the Written Description guidelines. A depiction of the invention has certainly been provided in Figures 1-7. Applicants note that three cases are cited in footnote 39 pertaining to the use of drawings pertaining to the adequacy of the Written Description Requirement. Specifically, footnote 39 states

> See, e.g., *Vas-Cath*, 935 F.2d at 1565, 19 USPQ2d at 1118 (``drawings alone may provide a `written description' of an invention as required by Sec. 112''); *In re Wolfensperger*, 302 F.2d 950, 133 USPQ 537 (CCPA 1962) (the drawings of applicant's specification provided sufficient written descriptive support for the claim limitation at issue); *Autogiro Co. of America v. United States*, 384 F.2d 391, 398, 155 USPQ 697, 703 (Ct. Cl. 1967) (``In those instances where a visual representation can flesh out words,drawings may be used in the same manner and with the same limitations as the specification.'').

Sufficient identifying characteristics of the constructs, compositions and kits of the present invention is provided as noted above in the specification. Additionally, a sufficient number of species have been disclosed. Finally, Applicants note that actual reduction to practice is not required to satisfy the Written Description Requirement. Footnote 36 of Written Description Guidelines state

> ....."The word 'invention' must refer to a concept that is complete, rather than merely one that is 'substantially complete.' It is true that reduction to practice ordinarily provides the best evidence that an invention is complete. But just because reduction to practice is sufficient evidence of completion, it does not follow that proof of

> reduction to practice is necessary in very case. Indeed, both the facts of the *Telephone Cases* and the facts of this case demonstrate that one can prove that an invention is complete and ready for patenting before it has actually been reduced to practice.

Therefore, the claimed invention is adequately described.

In view of the above arguments, Applicants assert that the rejection has been overcome. Applicants therefore request that the rejection under 35 U.S.C. 112, first paragraph (written description) be withdrawn.

The Rejections Under 35 U.S.C. 102(e)

Claims 246-270 have been rejected under 35 U.S.C. 102(e) as being anticipated by Meyer et al., U.S. Patent No. 5,574,142 (hereinafter "Meyer")). It is asserted that the claims still broadly read on a wide scope of possible nucleic acid constructs and that Meyer et al. teach non-naturally occurring constructs which produce an antisense product in the cell having the claimed limitations.

Applicants respectfully traverse the rejection. Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Foundation v. Genentech Inc.* 927 F.2d 1565, 18 USPQ2d 1001, 18 USPQ2d 1896 (Fed. Cir. 1991).

Applicants assert that the construct recited in claims 246-270 can be distinguished from Meyer. The ODN-peptide conjugates disclosed by Meyer et al. **are not** constructs as defined by the instant specification. Specifically, it is stated on page 7, last line to page 8, line12 that

> Another method for nucleic acid delivery is the introduction into cells of Primary Nucleic Acid Constructs which themselves do not act on cellular processes but which produce single stranded nucleic acid in the cell which acts on cellular processes. In this case the introduced Primary Nucleic Acid Construct can integrate into cellular nucleic acid or it can exist in an extrachromosomal state, and it can propagate copies of itself in either the integrated or the extrachromosomal state. The nucleic acid construct can produce, from promoter sequences in the Primary Nucleic Acid Construct, single stranded nucleic acids which affect cellular processes of gene expression and gene replication. Such nucleic acids include antisense nucleic acids, sense nucleic acids and transcripts that can be translated into protein. The intracellular concentrations of such nucleic acids are limited to promoter-dependent synthesis.

The ODN-peptide conjugates of Meyer et al. clearly are not constructs. This is because the conjugates cannot integrate into cellular nucleic acid or exist in an extrachromosomal state. The ODN-peptide conjugates certainly cannot propagate copies of itself in either the integrated or the extrachromosomal state. In other words, the ODN-peptide conjugates of Meyer et al. are not capable of self replication.

In view of the above arguments, Applicants assert that the rejections under 35 U.S.C. §102(e) have been overcome. Therefore, Applicants respectfully request that the rejections be withdrawn.

Summary and Conclusions

Claims 246-270 are presented for further examination. No claims have been amended, canceled or added by this paper.

This Amendment is being accompanied by a Request For An Extension Of Time (3 Months) and authorization for the fee therefor. No other fee or fee(s) are believed to be due for this Amendment. In the event that any other fee or fees are due, however, authorization is further given to charge the amount of any such fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,

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ANTISENSE RESEARCH AND DEVELOPMENT 4:145–146 (1994)
Mary Ann Liebert, Inc., Publishers

Editorial

Progress in Evaluation of the Potential of Antisense Technology

THE CENTRAL QUESTION ABOUT ANTISENSE TECHNOLOGY has never been whether the concept is exciting, but rather whether it would work. This question has been asked in many vernaculars depending on the background of the person asking the question, but it reduces to the issue of whether oligonucleotides will have satisfactory drug properties. Will they have appropriate pharmacologic, toxicologic, and pharmacokinetic properties to realize the potential of the antisense mechanism, and is there sufficient scope for medicinal chemistry to generate new analogs with improved properties? Although definitive answers to questions about the value of drugs of any sort must await broad clinical use after marketing, the answers we have today persuasively argue that the technology should be vigorously pursued and rigorously evaluated and may work as we hope. Virtually all the data that support this view derive from studies on phosphorothioates, but exciting new chemical classes are being tested and a number are in animal studies today.

Recently, we reported on the results of Phase I/II studies of intravitreally administered ISIS 2922 in AIDS patients with refractory CMV retinitis (Crooke, 1994; Palestine *et al.*, 1994). This study demonstrated that ISIS 2922 produced a dose-dependent inhibition of progression of CMV retinitis in patients who had failed all other CMV therapy, had median CD4 counts of 4, and had a median duration of CMV retinitis of 11 months. This study also demonstrated that the drug could be given once every other week with maintenance of prolonged remissions. The main drug-related adverse event was exacerbation of ocular inflammation. Armed with this information, we are initiating definitive clinical trials for this drug. This study is exciting because it is the first study to demonstrate clinical activity of an antisense oligonucleotide and because the drug resulted in rapid, meaningful responses in desperately ill patients with virtually no other recourse. Of course, we have not yet defined the value of ISIS 2922 in this disease. That awaits the completion of more definitive trials. Nor does this study guarantee that ISIS 2922 will be approved as therapy for this disease. Nor can be we prove that the principal mechanism of action of ISIS 2922 in this study is antisense. Further, the study was not designed to show that antisense oligonucleotides are active when administered systemically to humans. Nevertheless, taken in the context of all other available data, these results are very encouraging.

We have also recently reported data suggesting that ISIS 2105 when injected intradermally has apparent activity in both primary and surgical adjuvant therapy of genital warts. Again, we must do much more work before we know whether ISIS 2105 is indeed active or valuable in this disease, but we are encouraged by these data as well and are initiating a multiple dose surgical adjuvant Phase II trial to confirm the activity of the drug and determine whether it has sufficient value to be commercialized.

We have reported definitive pharmacokinetic studies on ISIS 2105 in rats after intravenous and intradermal doses (Cossum *et al.*, 1993, 1994). These studies clearly demonstrate excellent bioavailability, peripheral tissue distribution, and clearance that support once a day or every other day dosing. Similar results have been reported by the group at Dupont Merck (Sands *et al.*, 1994), and they have shown autoradiographic results showing drug inside cells in the liver and kidney. We and our colleagues at Ciba-Geigy have similar autoradiographic data, not yet published. Furthermore, we will shortly report definitive pharmacokinetic studies after intradermal dosing in man confirming that man and rats (as well as monkeys, mice, and rabbits) handle phosphorothioates similarly (Crooke *et al.*, 1994). These data are extremely important as they demonstrate attractive parenteral pharmacokinetic properties for phosphorothioate antisense drugs and show that for this class of drugs *in vitro* cell uptake studies do not predict *in vivo* behavior. This last point is not surprising as there is no class of drugs of which I am aware whose pharmacokinetic properties can be simply extrapolated from *in vitro* studies.

In a wide range of studies performed in our laboratories, Hybridon's and others, we have also defined the toxic liabilities of phosphorothioates. We believe the dose limiting toxicities will likely be related to effects on clotting, complement activation, or possibly cytokine release, and that the therapeutic index will be satisfactory. We will also shortly report studies that define the mechanisms underlying these effects.

Perhaps most importantly, however, we and many other laboratories have demonstrated potent systemic effects of phosphorothioates in animals in which all of the data are consistent with an antisense mechanism (Hiltiva *et al.*, 1994; Shoraki *et al.*, 1994). In our laboratories and those of our collaborators, we have shown potent antisense activities against Ha-RAS, Ki-RAS, PKC-α, RAF kinase, ICAM-1 and other targets. In several cases, we have unequivocally proven mechanism by showing a selective loss of target RNA in various tissues at doses ranging from less than 1 mg/kg to 20 mg/kg daily. Interestingly, because the cells that expressed many of the targets listed above did not take up sufficient oligonucleotide, we had to employ cationic lipid transfection to show *in vitro* activity. *In vivo*, no

specialized delivery system was required. In a particularly important series of studies, Dean *et al.* (1994) have shown potent systemic isotype selective loss of PKC-α RNA induced by a phosphorothioate oligonucleotide and shown 24-hour duration of effects and absence of toxhyphylaxis.

In aggregate, all of the data encourage cautious optimism.

So does this mean that the "bullets are really magic"? In my view, this question epitomizes one of the causes of cynicism regarding antisense technology. We are developing a new pharmacological and chemical class of drugs. That we are simultaneously creating a new technology and trying to develop drugs from this technology is entirely appropriate and the only real way to understand the drug properties of these molecules. We hope these drugs will be of unique value. They are, nevertheless, drugs. We expect them to have a variety of effects, but if we can understand these properties in the context of modern pharmacology and antisense drugs continue to perform as well as they have to date, then patients will benefit. With these drugs, as with all other classes of drugs, there will be questions that cannot be answered. However, we have already generated more *direct* proof of mechanism of action in animals than for many more established classes of drugs, and the pharmacokinetic and toxicologic properties appear, at present, to be reasonably attractive.

That there are questions that we cannot answer definitively should not be cause for despair. Do we know the precise mechanisms that explain aspirin uptake into cells? Do we understand, at a biochemical level, how aspirin disproportionates between serum protein binding sites and peripheral tissues? For how many classes of drugs do we have unequivocal direct proof of mechanism of action in animals or man?

I would urge continuing critical evaluation of antisense technology. We need to continue to try to understand these drugs. We expect that we will find limits to their utility. For example, we already know that phosphorothioates do not cross an intact blood brain barrier and are minimally orally bioavailable. We may even unearth effects that negate the potential of this technology entirely. However, the data to date are encouraging, and the technology has successfully overcome a large number of hurdles in a relatively short time.

On the other hand, I would hope for an end to the cynicism about antisense technology. This begins with asking the right questions in the right way. The right questions pertain to factors influencing therapeutic index and the breadth and ease of therapeutic use. The right way to ask the questions is in the context of modern pharmacology and in carefully controlled experiments in which dose response curves for various effects are critically defined.

In short, we must set reasonable expectations for this technology, evaluate its potential reasonably and report our results with integrity. If we do this, we will meet our responsibilities to the technology, to patients in need, and, for those of us in commercial organizations, to investors.

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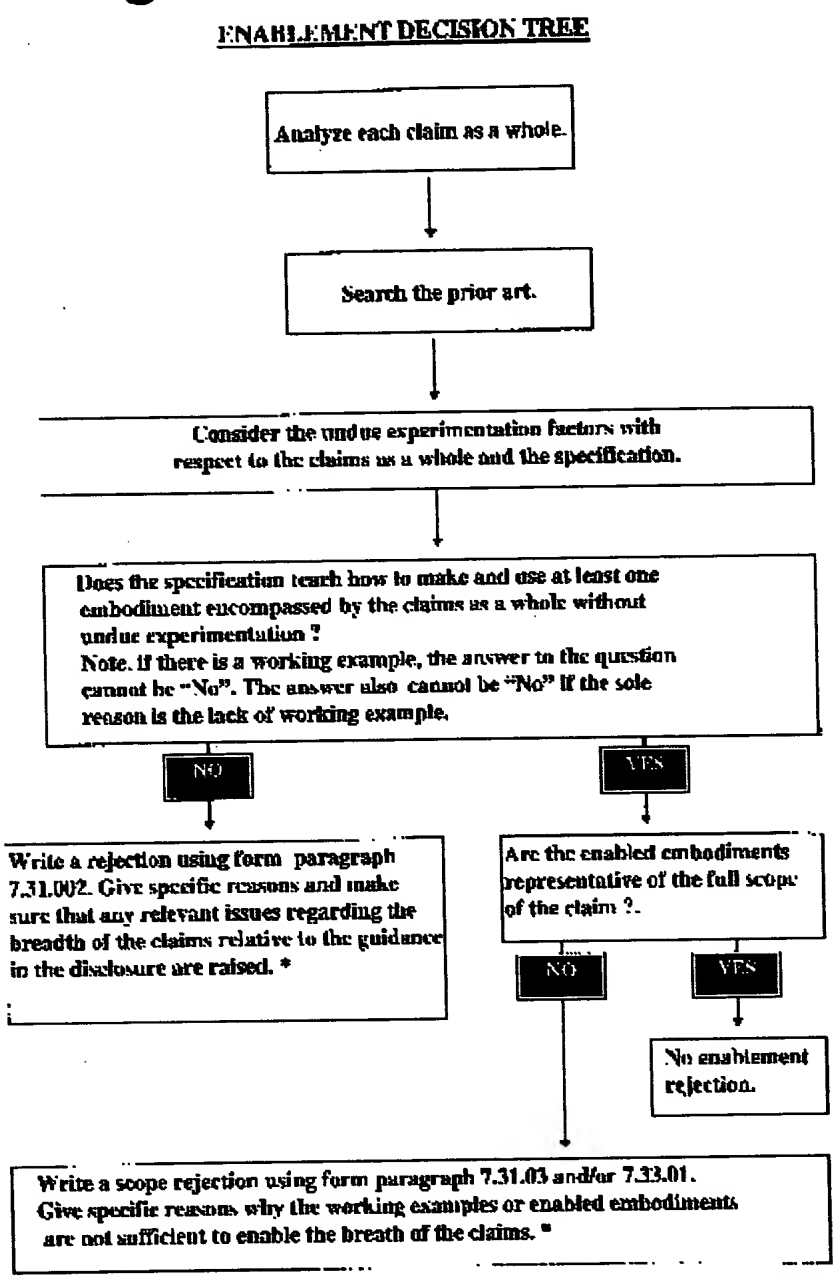

Examp * If specific technical reasons cannot be given or properly supported with sufficient evidence, then the answer to the previous question should have been "yes".

Example A: Hybridization Probes I

Specification: The specification discloses that bacteria A is known to cause a specific disease and, therefore, detection of bacteria A in a sample is desirable. The specification even discloses that methods are known which detect bacteria A in a sample via culturing techniques. According to the specification, such detection methods are difficult to perform and therefore detection methods using nucleic acid probes are preferred.

The specification discloses that one object of the invention is to provide nucleic acids complementary to unique nucleic acid sequences within the RNA or DNA of bacteria A and which can be used to detect bacteria A. Another object of the invention is to provide a method of detecting bacteria A in a